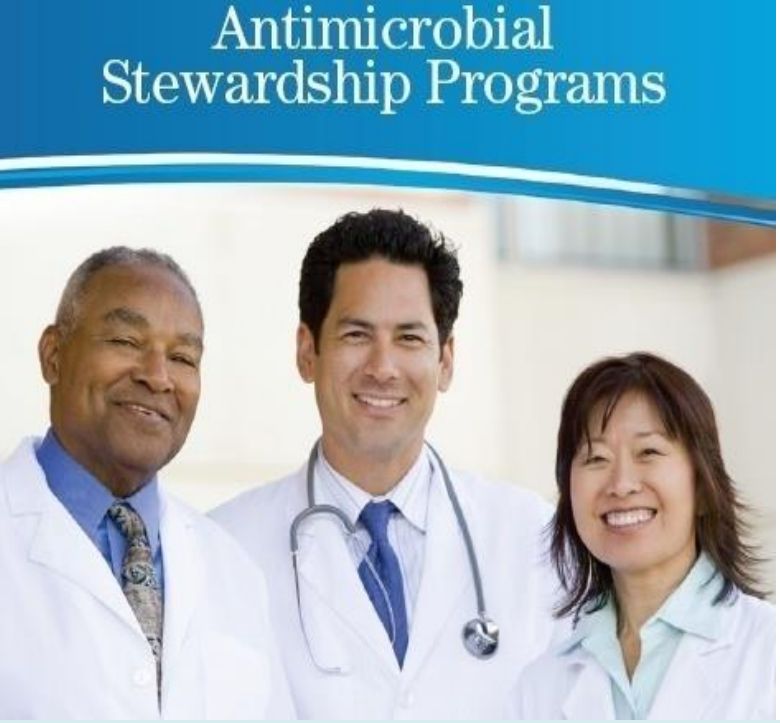


Antimicrobial Stewardship:

Arizona Partnerships Working to Improve the Use of Antimicrobials in the Hospital and Community

Part 1

"Antibacterials – indeed, anti-infectives as a whole – are unique in that misuse of these agents can have a negative effect on society at large. Misuse of antibacterials has led to the development of bacterial resistance, whereas misuse of a cardiovascular drug harms only the one patient, not causing a societal consequence."

- Glenn Tillotson; Clin Infect Dis. 2010;51:752

"…we hold closely the principles that antibiotics are a gift to us from prior generations and that we have a moral obligation to ensure that this global treasure is available for our children and future generations."

- David Gilbert, et al (and the Infectious Diseases Society of America). Clin Infect Dis. 2010;51:754-5

A Note To Our Readers and Slide Presenters

The objectives of the Subcommittee on Antimicrobial Stewardship Programs are directed at education, presentation, and identification of resources for clinicians to create toolkits of strategies that will assist clinicians with understanding, implementing, measuring, and maintaining antimicrobial stewardship programs.

The slide compendium was developed by the Subcommittee on Antimicrobial Stewardship Programs (ASP) of the Arizona Healthcare-Associated Infection (HAI) Advisory Committee in 2012-2013.

ASP is a multidisciplinary committee representing various healthcare disciplines working to define and provide guidance for establishing and maintaining an antimicrobial stewardship programs within acute care and long-term care institutions and in the community.

Their work was guided by the best available evidence at the time although the subject matter encompassed thousands of references. Accordingly, the Subcommittee selectively used examples from the published literature to provide guidance and evidenced-based criteria regarding antimicrobial stewardship. The slide compendium reflects consensus on criteria which the HAI Advisory Committee deems to represent prudent practice.

Disclaimers

All scientific and technical material included in the slide compendium applied rigorous scientific standards and peer review by the Subcommittee on Antimicrobial Stewardship Programs to ensure the accuracy and reliability of the data. The Subcommittee reviewed hundreds of published studies for the purposes of defining antimicrobial stewardship for Arizonan clinicians. The Arizona Department of Health Services (ADHS) and members of its subcommittees assume no responsibility for the opinions and interpretations of the data from published studies selected for inclusion in the slide compendium.

ADHS routinely seeks the input of highly qualified peer reviewers on the propriety, accuracy, completeness, and quality (including objectivity, utility, and integrity) of its materials. Although the specific application of peer review throughout the scientific process may vary, the overall goal is to obtain an objective evaluation of scientific information from its fellow scientists, consultants, and Committees.

Please credit ADHS for development of its slides and other tools. Please provide a link to the ADHS website when these material are used.

Introduction to Slide Section

- **Preface:**

  Seven reasons to optimize antimicrobial therapy are discussed with focus on selection of antibiotic resistance, the lack of new drug development to combat bacterial resistance mechanisms, health and economic outcomes of bacterial resistance, the need to educate clinicians on optimal prescribing of antimicrobials, the increasing awareness of the impact of resistance by government, professional societies and the lay public.

- **Content:**

  Main presentation is 44 slides, with 8 back-up slides. With the subtitle slides excluded, this presentation can be completed within 45-60 minutes.

- **Suggestions for Presentation:**

  The intended audience includes prescribers, administrators, and other healthcare workers. This section serves to orient the audience to the challenges of suboptimal antimicrobial drug use, including adverse events and healthcare economics. It also outlines for administrators the threats of resistance and might be used to obtain support for an ASP.

- **Comments:**

  These slides could be combined with part 3 “Antimicrobial Stewardship: Making the Case” or part 10 “Barriers and Challenges”.

REASONS TO OPTIMIZE ANTIBIOTIC USE

Many Reasons to Improve Antibiotic Use

- Antibiotic resistance is a result of antibiotic overuse – nature's perfect selection process in rapid action
- Antibiotic resistance impacts clinical outcomes and thereby it is also a patient safety issue
- Bacterial resistance impacts medical resources because most hospital-acquired infections (HAIs) are caused by drug-resistant bacteria
- Many hospital-acquired infections are not reimbursed by the Centers for Medicare and Medicaid (CMS)
  - Private insurers are following suit as "value-based purchasing" and "risk sharing models" become industry-wide

Words to Heed From Decades Past

"The public will demand [the drug and]…then will begin an era…of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted."

Sir Alexander Fleming. Penicillin's finder assays its future. New York Times 1945; 21.

REASONS TO OPTIMIZE ANTIBIOTIC USE:

1. SELECTION OF RESISTANT PATHOGENS

Associations Between Antibiotic Use and the Emergence of Resistance

- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance
- Resistance is more common in health care-associated bacterial infections compared with community-acquired
- When compared with controls, patients harboring resistant organisms are more likely to have received prior antimicrobials
- Areas within hospitals (i.e. critical care units) that have the greatest rate of antimicrobial resistance also have the greatest rate of antimicrobial use
- Increasing the duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms

Tracking Key Pathogens:

Current Causes of the Majority of US Hospital Infections Which Effectively "Escape" the Effects of Antibacterial Drugs

E	*Enterococcus faecium* (VRE)
S	*Staphylococcus aureus* (MRSA)
K	*Klebsiella pneumoniae* (ESBL-producing *E.coli* and *Klebsiella* species; *Klebsiella pneumoniae* carbapenem hydrolyzing beta-lactamases, KPC)
A	*Acinetobacter baumannii*
P	*Pseudomonas aeruginosa*
E	*Enterobacter* species

Hospital-acquired infections

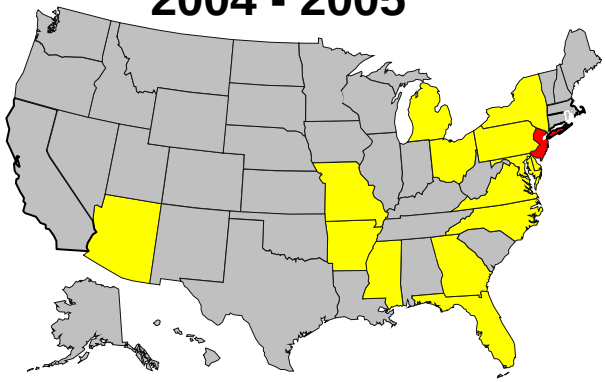
- These 6 groups of bacteria currently cause the majority of hospital infections and effectively "escape" the effects of antibiotics
- Some strains have become resistant to all antibiotics
- Therapeutic options for these pathogens are so extremely limited that clinicians are forced to use older, and more toxic drugs, such as colistin
- This list does not include important evolving pathogens, such as fungi, *Clostridium difficile*, metallo-beta-lactamase-producing Gram-negatives, colistin-resistant *A.* baumannii, and vancomycin-resistant *S. aureus* (VRSA)

Boucher H, et al. Clin Infect Dis. 2009;48:1-12

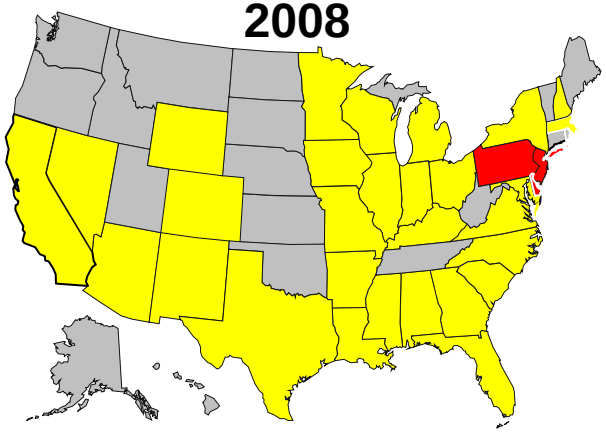
Emergence of Resistance Can Be Rapid and Alarming: The Case of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP)[1,2]

- First described in North Carolina in 1999
- CRKP has been identified in 24 states and is recovered routinely in certain hospitals in New York and New Jersey
- Analysis of 2007 data regarding health-care–associated infections reported to CDC indicated that 8% of all *Klebsiella* isolates were CRKP, compared with fewer than 1% in 2000 (CDC, unpublished data, 2008). The rise of KPCs was rapid between 2000 and 2010
- Facilitated by inability to detect isolates with low-level resistance by current breakpoints

2004 - 2005



2008



No reports to CDC

Sporadic isolate(s)

Frequent/Widespread Occurrence

1 CDC.MMWR.March 20, 2009;58(10):256-60.
2 Landman D et al. J Clin Microbiol. 2010;48(12):4604-7.

Endemicity/epidemics of KPCs in Puerto Rico by 2008 not shown in maps

The Selection of Bacteria Resistant to Powerful Antibiotics Occurs Rapidly

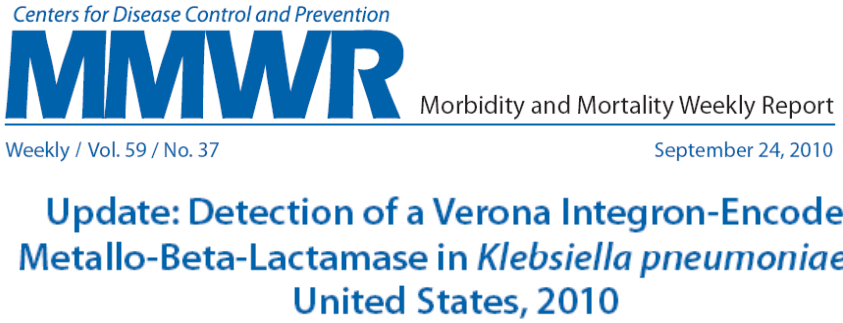
- Rise in ESBL-producing *Klebsiella pneumoniae* observed in 500-bed university-affiliated community hospital in Queens, NY
- Restriction of IV and PO cephalosporins (with 5 exceptions) in 1996
- Compared ESBL infection and colonization rates between 1995 and 1996
- Imipenem was used for the treatment of ESBL-producing *K.pneumoniae* infections
- Results of cephalosporin restriction:
  - 80% reduction in hospital-wide use of cephalosporins
  - 141% increase in imipenem use
  - 44% reduction in the incidence of ceftazidime-R *K.pneumoniae* overall
  - 71% reduction within all ICUs
- At the end of the restriction period, a concomitant 69% increase in the incidence of imipenem-resistant *Pseudomonas aeruginosa* occurred throughout the medical center

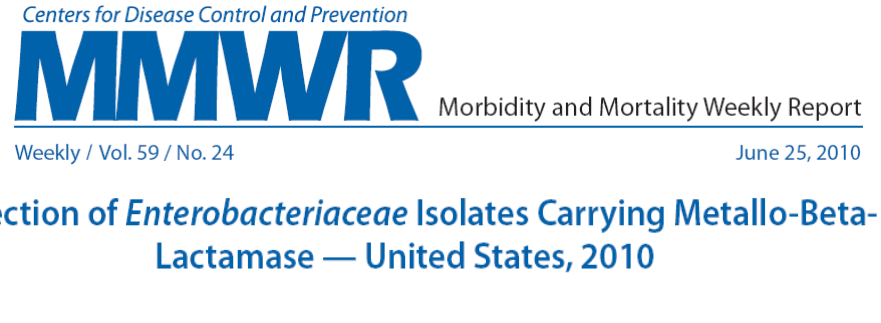
When you divide every 15 minutes, it is easy to overcome antibiotic pressure

Rahal JJ, et al. JAMA. 1998;280:1233-7

Antibiotics and Bacterial Resistance: "Tragedy of the Commons"

- Antibiotics exist as a valuable resource for all
- Antibiotic therapy can cure an infection in a single person
- Overuse of the resource amongst a population leads to antibiotic resistance
- Antibiotic resistance restricts the value of the resource
- The resource becomes depleted as choices of antibiotics become limited
- No new novel antibiotics effective against MDROs
- Antibiotics exist no longer as a resource to treat infections





Predicted Issues in Gram-Negative Bacteria Resistance in the Next Decade

- Widespread occurrence of carbapenem resistance in hospitalized patients necessitating “routine” use of polymyxins or tigecycline
- Resistance to polymyxins and tigecycline commonplace in some hospitals
- Loss of improvement in intensive care unit survival rates due to impact of resistance in Gram-negative bacilli
- Calls for universal screening for multidrug-resistant gram-negative bacilli at hospital admission
- Increased acquisition of carbapenem-resistant organisms outside of hospitals
- Increased hospitalizations for community-onset urinary tract infections due to pathogens resistant to all orally administered antibiotics

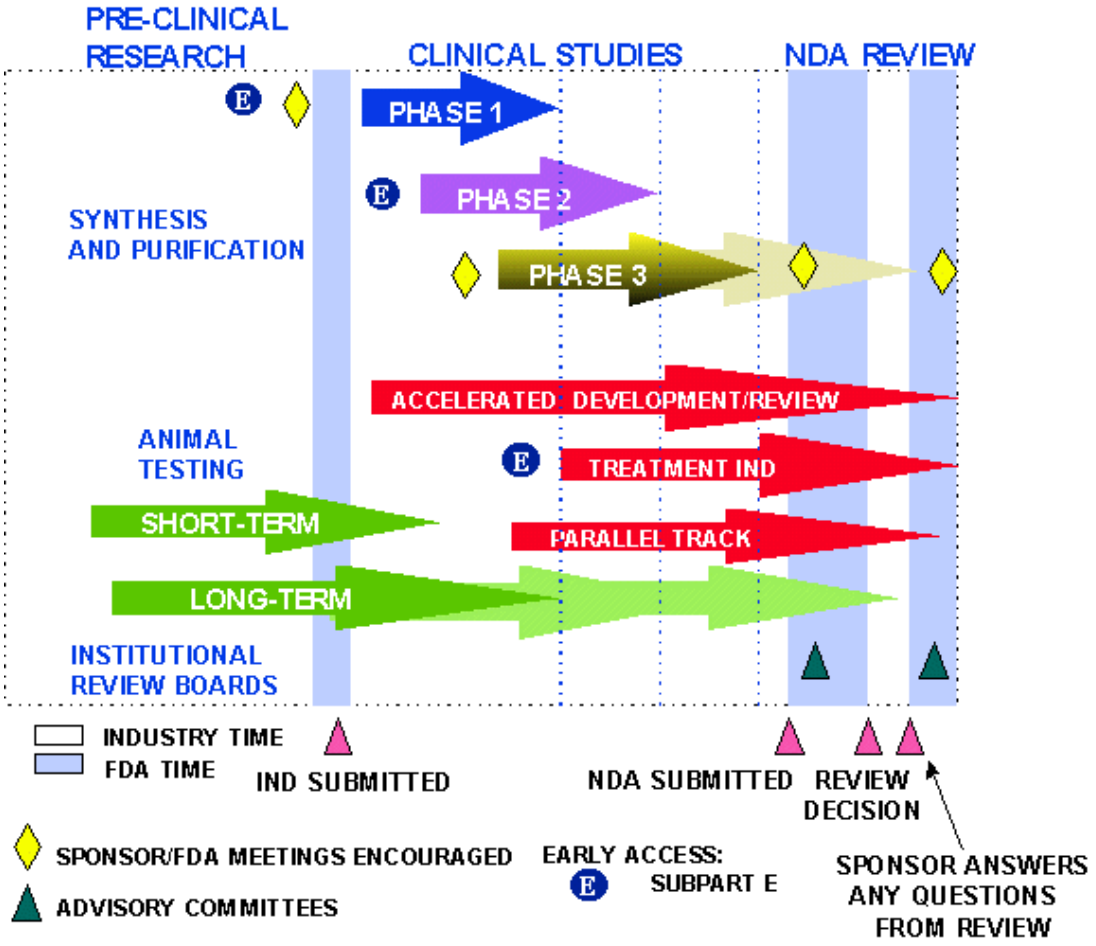
Paterson D, Rogers B. Clin Infect Dis. 2010;51:1245-7

REASONS TO OPTIMIZE ANTIBIOTIC USE:

2. WHERE DID ANTIBIOTIC DEVELOPMENT GO?

Antibiotic Drug Development: Costly and Time-Consuming

- For new molecular entities which were antibiotics, approved by the FDA between 2003 to 2007, the clinical development phase (IND filing to NDA submission) was 6.0 years and the approval phase (NDA submission to approval) was 1.7 years [1]
- $100 million is spent for a phase III clinical trial program for each planned disease state indication [2]
- At the time of discovery, the net present value of antibiotic to a drug company is MINUS $50 million. That compares to a positive $1 billion for a new musculoskeletal drug [2]

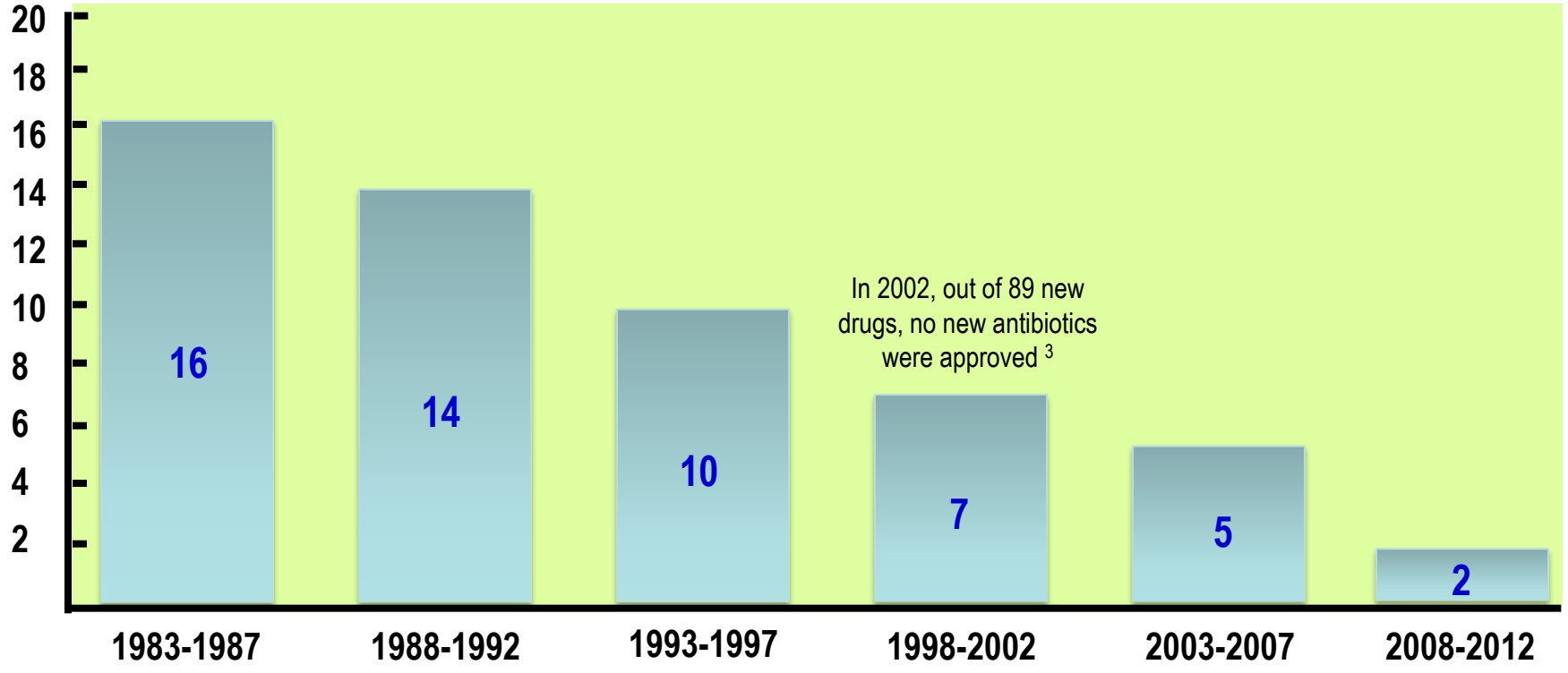


1 Kaitin K. Nature. 2010;87(3):356-61.
2 Spellberg B. APUA Newsletter. 2011;30(1)

Decline in the Number of New Antibacterial Agents Approved in the USA, 1983-2012[1]

Number of Systemic Antibiotics Approved by the FDA in 5-Year Increments

Since 1983, the FDA has approved 62 to 142 New Drug Applications (NDAs) and 14 to 53 New Molecular Entities (NMEs) EACH YEAR [2]



1 Boucher H et al. *Clin Infect Dis* 2009;48:1-12 (up to 2007)
2 http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm
3 Infectious Diseases Society of America. *Bad Bugs, No Drugs*. July 2004. Available at: www.idsociety.org
4 Boucher H et al. *Clin Infect Dis.* 2013;56:1685-94

The Antibiotic Pipeline is Dry

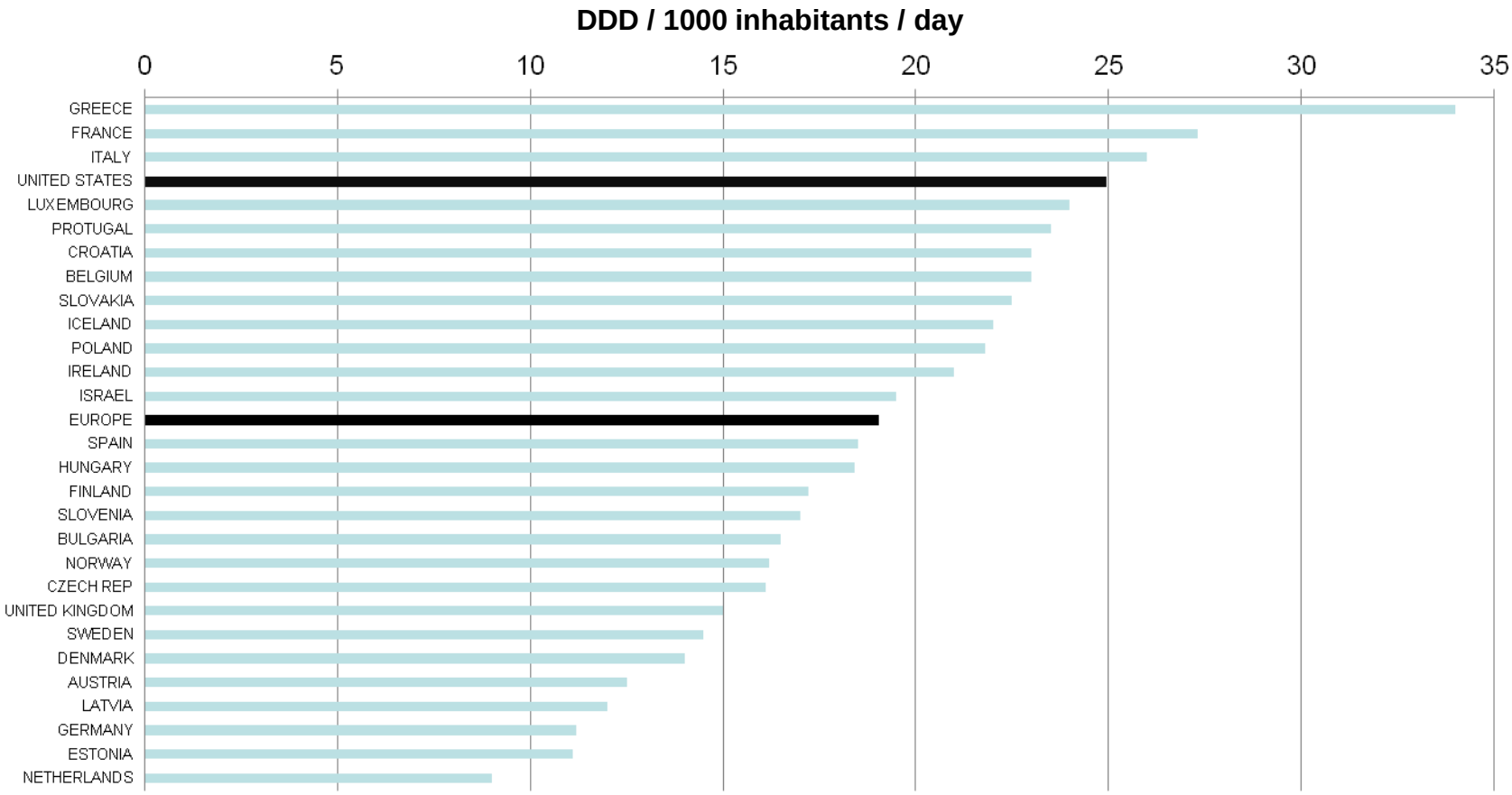
- Only 2 new antibiotics have been approved since the Infectious Diseases Society of America's (IDSA's) 2009 pipeline status report, and the number of new antibiotics annually approved for marketing in the United States continues to decline
- Since 2009, only 16 antibiotics for systemic infections were in development
- Only seven of these have activity against key Gram-negative bacteria
  - None of these agents was included in the 2009 list of antibacterial compounds in phase 2 or later development, and none addresses the entire spectrum of clinically relevant Gram-negative resistance
  - None have activity against bacteria resistant to all current antibiotics

Talbot G et al. Clin Infect Dis. 2006;42:657-68; Boucher H et al. Clin Infect Dis. 2009;48:1-12; Infectious Diseases Society of America (IDSA); Spellberg B, Blaser M, et al. Clin Infect Dis 2011; 52(suppl 5):S397–428; Boucher H et al. Clin Infect Dis. 2013;56(12):1685-94

REASONS TO OPTIMIZE ANTIBIOTIC USE:

3. ANTIBIOTIC USE IS SUBOPTIMAL

Total Outpatient Antibacterial Use in the United States and 27 European Countries in 2004

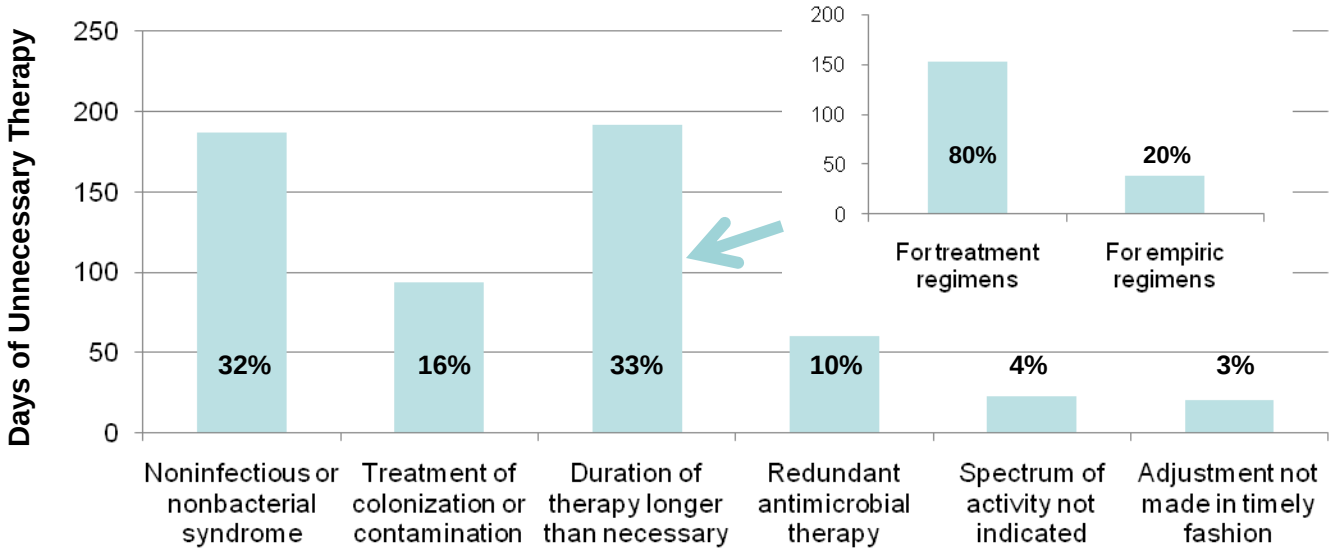


Comparative Use (DDD/1,000 inhabitants/day):
United States, 24.9; Europe, 19.0

DDD = defined daily dose. Methodology applied to IMS Health data, USA, 2004.
Adapted from: Goossens H et al. Clin Infect Dis. 2007;44:1091-5; erratum, Clin Infect Dis. 2007;44:1259.

Excessive Use of Antibiotics

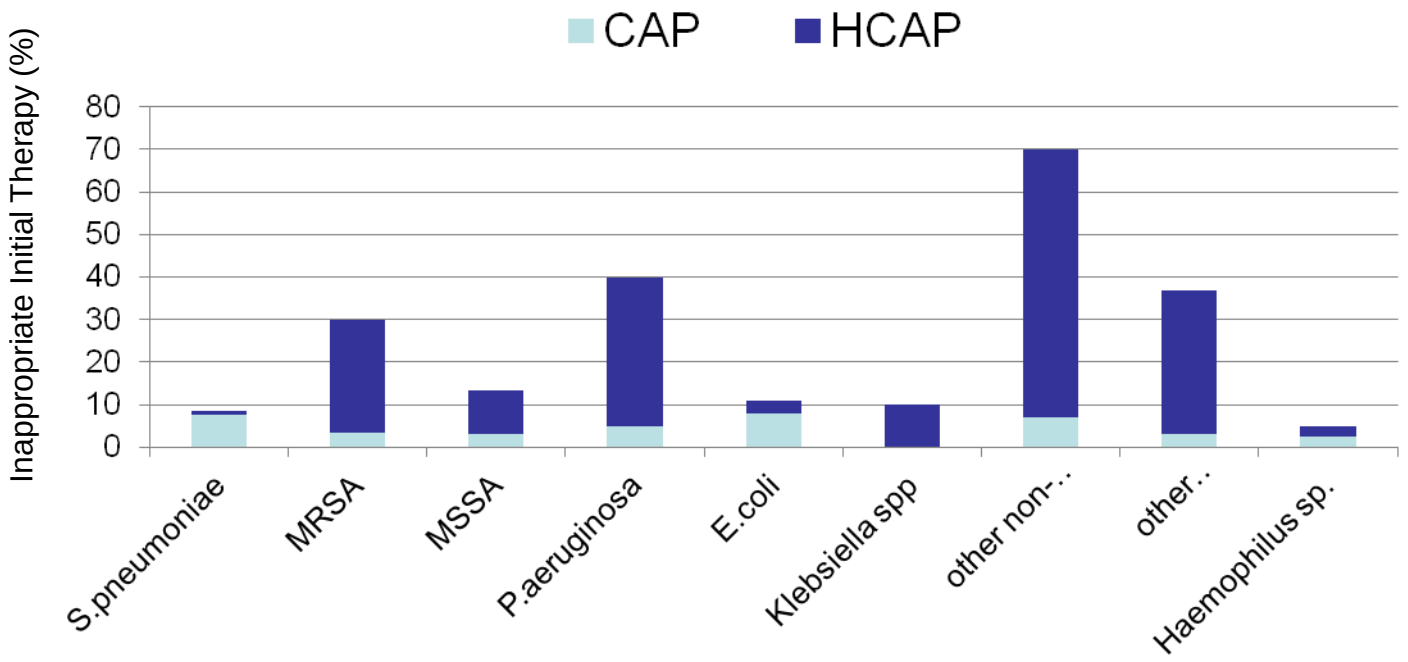
- Prospective observational study in a 650-bed university-affiliated hospital of adult non-ICU care inpatients; new antimicrobials examined over a 2-week period
- Results:
  - 1,941 days of antimicrobial therapy in 129 patients
  - 576 (30%) of 1,941 days of therapy were deemed unnecessary
  - Total average wholesale price (AWP) of all unnecessary antimicrobials prescribed for the study patients was $14,600, corresponding to an estimated yearly AWP of $350,400



Hecker M et al. Arch Int Med. 2003;163:972-8

Rates of Inappropriate Antibiotics in Patients with CAP or HCAP* by Pathogen Distribution

Administration of inappropriate initial antimicrobial treatment was statistically more common among HCAP patients (28.3% versus 13.0%; P < 0.001)



Of the 220 patients initially treated only with a CAP regimen (ceftriaxone plus azithromycin, or moxifloxacin), 49 (22.3%) initially received inappropriate antimicrobial treatment (CAP, 15 [13.6%] versus HCAP, 34 [30.9%]; P=0.002).

* HCAP = healthcare-associated pneumonia

Adapted from: Micek S et al. Antimicrob Agents Chemother. 2007;51:3568-73.
Shorr A, Owens R. Am J Health-Syst Pharm. 2009;66(suppl 4):S8-14.

Asymptomatic Bacteruria (ASB): Frequently Treated Unnecessarily

Study	Patient Population	Lack of Adherence to Guidelines
Dalen et al, 2005	• Ottawa hospital • 29 patients with catheter-associated ASB	52% prescribed antimicrobials inappropriately
Gandhi et al, 2009	• University of Michigan • 49 patients with UTI diagnosed	32.6% did not meet criteria for UTI (most due to lack of symptoms)
Cope et al, 2009	• Houston VA • 164 episodes of catheter-associated ASB	32% prescribed antimicrobials inappropriately

Dalen DM et al. Can J Infect Dis Med Microbiol. 2005;16:166.
Gandhi T et al. Infect Control Hosp Epidemiol. 2009;30:193.
Cope M et al. Clin Infect Dis. 2009;48:1182.

Factors That Lead to Inappropriate Use of Antibiotics

Internal

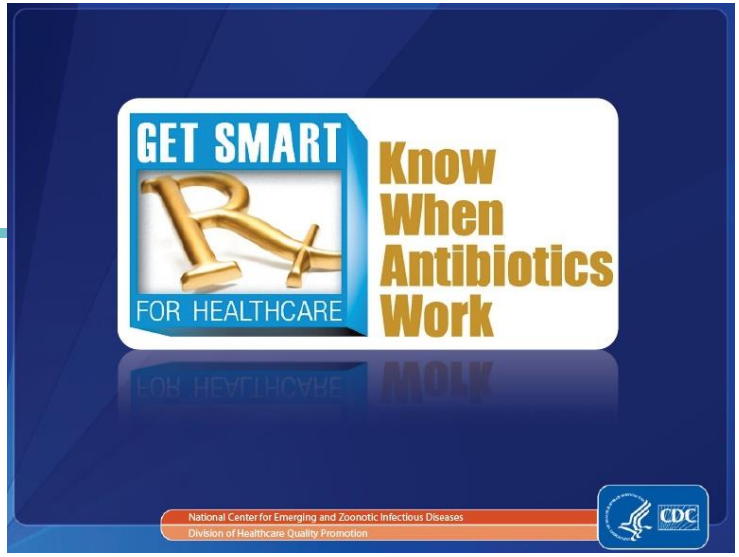
- Lack of knowledge of infectious diseases, e.g., “more antibiotics are better”
- “Double coverage is better for killing”
- “Expanding” spectrum when consolidation is better
- Lack of knowledge about antibiotic spectrum of activity, e.g., “broader is easier (to prescribe) – one regimen for everything”
- Lack of knowledge about dosing, e.g., “low dose for longer is better”
- Lack of knowledge of antibiotic allergies and their implications
- Lack of knowledge about when to give and stop antibiotics
- Prophylaxis outside of surgical theater

External

- Lack of time to educate patients and prescribers about when antibiotics are not indicated
- Lack of microbiologic data (and acquisition of it)
- Fear of malpractice for not giving an antibiotic
- Misperception that antibiotics have only benefit and no harm
- Pharmaceutical detailing - new does not always equal better
- Critical access hospitals may not have availability of ID specialists

"Doctor, Can You Answer This?" Education Is Awareness

- How many patients last year grew vancomycin-resistant enterococci (VRE) from a non-urinary source at our hospital?
- Name 3 oral agents which target MRSA besides linezolid (Zyvox)
- Piperacillin-tazobactam (Zosyn) does not cover anaerobes: T or F?
- Resistance to ciprofloxacin in *E.coli* from the most recent antibiogram was _____%?
- *Clostridium difficile* infection is mostly due to prolonged antibiotic use with disruption of normal protective GI flora: T or F?
- Always treat asymptomatic bacteruria because it can lead to urosepsis: T or F?
- Can you effectively treat mild-to-moderate hospitalized community-acquired pneumonia (CAP) with less than 7 days therapy?



Slide set available at: http://www.cdc.gov/getsmart/healthcare/inpatient-stewardship.html (accessed July 22, 2013)

- What are the established drug regimens for treatment of community-acquired pneumonia?
- The attributable cost of a single CLA-BSI episode in 2009 at our hospital was $ _____
- Vancomycin is as effective as cefazolin or nafcillin in treating an infection due to MSSA: T or F?
- The institution has specific recommendations for changing IV antibiotics to PO equivalents: T or F?

REASONS TO OPTIMIZE ANTIBIOTIC USE:

4. ANTIBIOTIC OVERUSE AND ENSUING RESISTANCE IMPACTS HEALTH & ECONOMIC OUTCOMES

Antibiotic Use, Costs, and Financial Outcomes

- Annually in the United States
  - 30% hospital admissions due to infection [1]
  - 2 million people develop HAI [2]
- 30-50% hospitalized patients receive antibiotics [1,2]
- Yet up to 50% of antibiotic orders are unnecessary or inappropriate [1-3]

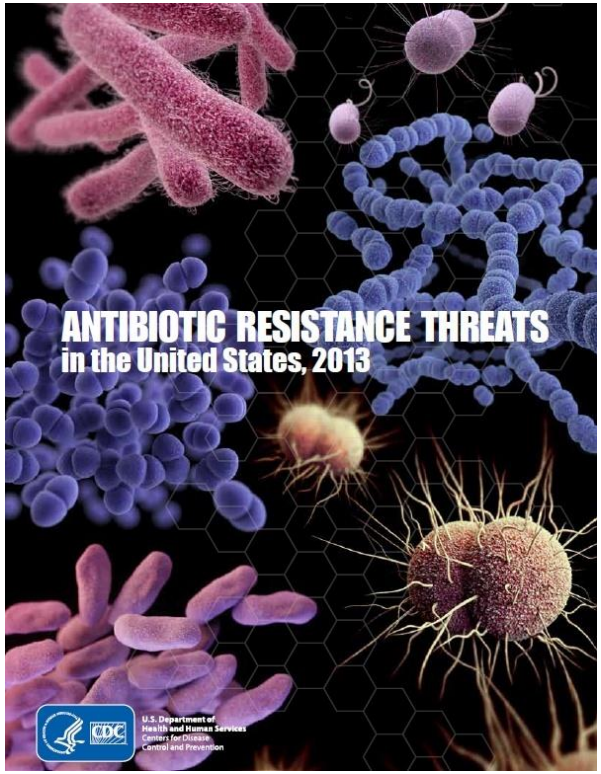
- 30% of hospital pharmacy budget is composed of antimicrobials [4]
- > $1.1 billion spent annually on unnecessary antibiotic prescriptions for respiratory infections in adults [5]

- $15 million to treat 188 cases of ABX resistant infections [5]
- Attributable costs (per episode) [4]
  - MRSA: $9,275 to $13,901
  - VRE: $27,190
  - Resistant *Enterobacter*: $29,379

1 Gums JG et al. Pharmacotherapy 1999;19:1369-77. 2 Owens Jr RC et al. Pharmacotherapy 2004;24:896-908.
3 Arnold FW et al. J Manag Care Pharm 2004;10:152-58. 4 Dellit TH et al. Clin Infect Dis 2007;44:159-77.
5 www.cdc.gov/getsmart/healthcare/inpatient-stewardship.html

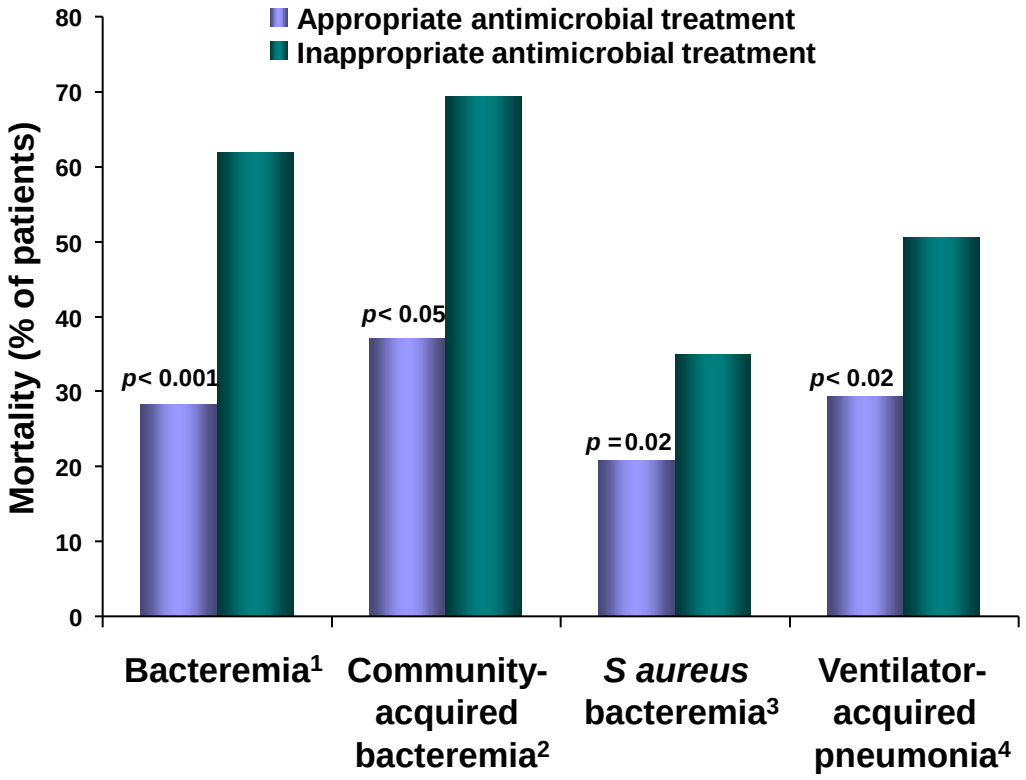
Reasons to Optimize Antibiotic Use: Clinical and Economic Consequences

- CDC recently provided conservative estimates that in the U.S., more than 2 million people are sickened every year with antibiotic-resistant infections, with at least 37,000 dying as a direct result with many more succumbing to other conditions complicated by an antibiotic-resistant infection or *C. difficile* infection
- The total economic cost of antibiotic resistance to the U.S. economy is estimated as high as $20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as $35 billion a year (2008 dollars).
- Up to 50% of all antibiotics prescribed are unnecessary or not optimally effective as prescribed
- One of four core actions that will help fight these deadly infections includes **improving the use of antibiotics**



CDC "Antibiotic Resistance Threats in the United States, 2013"
Available at: http://www.cdc.gov/drugresistance/threat-report-2013/

Impact of Inappropriate Initial Empiric Antibiotic Selection



- Studies have demonstrated that inappropriate initial therapy is an important independent determinant of mortality[1-4]
- Inappropriate initial antimicrobial therapy is defined as the use of an agent or agents to which the isolated pathogens are later determined to be non-susceptible[5]

Drug resistance hinders selection of effective empiric therapy

1 Ibrahim EH, et al. Chest. 2000;118:146-155. 2 Valles J, et al. Chest. 2003;123:1615-1624. 3 Khatib R, et al. Eur J Clin Microbiol Infect Dis 2006;25:181-185. 4 Teixeira PJZ, et al. J Hosp Infect 2007;65:361-367. 5 The American Thoracic Society and the Infectious Diseases Society of America. Am J Respir Crit Care Med 2005;171:388-416.

Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital

- In a random sample of high-risk hospitalized adult patients (n=1,391) during calendar year 2000, 13.5% had an antimicrobial-resistant infection (ARI)
- Patients with an ARI (case) were propensity score-matched to patients without ARI (control); both community- and hospital-acquired infections were included
- ~70% of patients with an ARI were defined as having an HAI by CDC definition
- Medical costs (2008 dollars) were measured from the hospital perspective
  - Medical costs attributable to ARI ranged from $18,588 to $29,069 per patient
  - Excess duration of hospital stay was 6.4 to 12.7 days
  - Attributable mortality was 6.5%
- Lowering ARI rate from 13.5% to 10% was estimated to save ~$1 million per year in medical costs

Roberts R, et al. Clin Infect Dis. 2009;49:1175-84

Antibiotic Misuse Adversely Impacts Patients: *Clostridium difficile* Infection (CDI)

- CDI is problematic when three factors are aligned:
  - Coexisting co-morbidities, including advanced age, renal dysfunction, or immunosuppression
  - Disturbed intestinal microbiota as a result of antibiotic therapy
  - Exposure to vegetative cells or spores of *C. difficile*
- Antibiotic exposure is the single most important risk factor for the development of CDI
  - Antibiotic exposure increases risk of CDI by 7- to 10-fold for up to 30 days post-exposure and for up to 3-fold for the next 60 days[1]
  - Up to 85% of patients with CDI have received an antibiotic in the 28 days prior to infection[2]

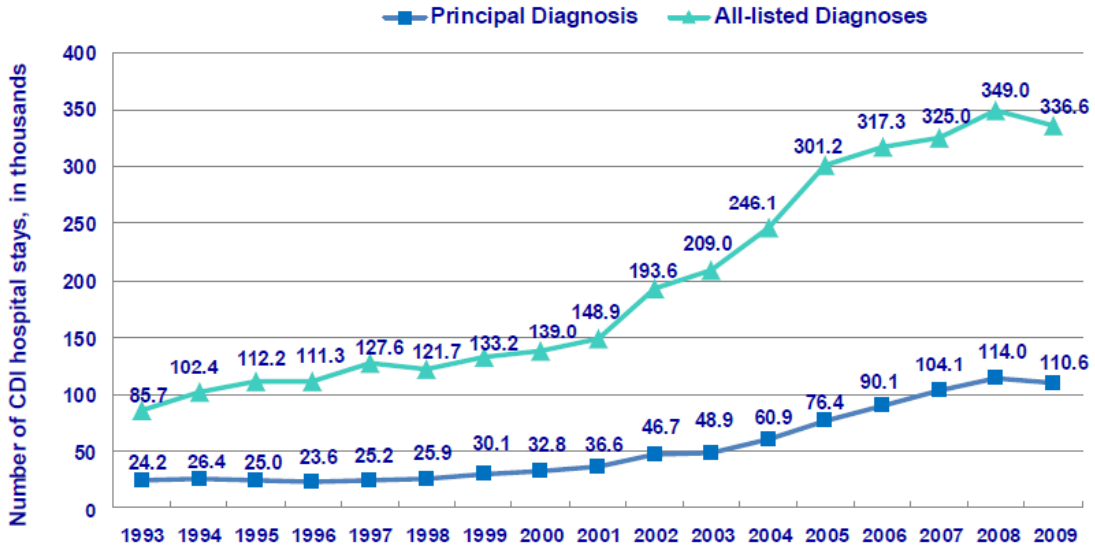
1 Hensgens M et al. J Antimicrob Chemother. 2012;67:742-8.
2 Chang H et al. Infect Control Hosp Epidemiol. 2007;28:926-31.

Clostridium difficile Infection Inpatient Cases Increased Significantly Starting in 2001

Incidence and Mortality

- Total incidence ~700K cases per year, including long-term acute care hospitals (LTACHs) and outpatient cases[1,2,3]
- In 2009, there were 336,600 CDI-related hospital stays in the U.S., or 0.9% of all hospital stays [1,4]
- Approximately 9.1% of CDI stays ended in death, compared with less than 2% for all other inpatients[4]
- Since 2003, more severe cases of CDI with mortality rates as high as 17% have been identified at several US and Canadian hospitals[5]

Trends in Hospital Stays Associated with *Clostridium difficile* Infection (CDI), 1993-2009[4] (ICD-9-CM 008.45)



The number of hospital stays associated with CDI more than doubled from 2001 to 2005; hospital stays with CDI increased four-fold over this 16-year time period

[1] AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 1993–2009

[2] Centers for Disease Control (CDC) website. Available at: http://www.cdc.gov/HAI/pdfs/toolkits/CDItoolkitwhite_clearance_edits.pdf. Accessed May 21, 2011.

[3] Internal estimates based upon AMR/Arlington Medical Resources, Inc., and Decision Resources, Inc. 2009. Hospital Anti-Infectives Insight Series: *Clostridium Difficile*

[4] Lucado et al. *HCUP Statistical Brief*. #124. January 2012;50:1-12.

[5] Pepin et al. *CMAJ.* 2004;171(5):466-472.

Antibiotics Are Not Harmless: Antibiotic-Related Adverse Drug Reactions

- National Injury Surveillance System (2004-2006)
- An estimated 142,505 visits (95% confidence interval [CI], 116,506–168,504 visits) annually were made to US emergency departments (EDs) for drug-related adverse events attributable to systemic antibiotics
- Antibiotics implicated in 19.3% of all ED visits for drug-related adverse events
- Most ED visits for antibiotic-associated adverse events were for allergic reactions (78.7% of visits; 95% CI, 75.3%–82.1% of visits)
  - Almost 50% of ED visits were associated with penicillins and cephalosporins
  - Sulfonamides associated with the highest rate of serious allergic reactions
  - 50% of all reactions were due to sulfonamides and clindamycin
  - Sulfonamides and fluoroquinolones were associated with the highest rate of neurological events
- Most prescriptions were for upper respiratory infections, chronic obstructive pulmonary disease (COPD), otitis media, and sinusitis

Shehab N et al. Clin Infect Dis. 2008;47(6):735-43

Antibiotic Resistance Can Be Considered an Adverse Event

ASHP definition of an adverse event:

- "Any unexpected, unintended, undesired, or excessive response to a drug that: 1) requires discontinuing the drug (therapeutic or diagnostic); 2) requires changing the drug therapy; 3) requires modifying the dose (except for minor dosage adjustments); 4) necessitates admission to a hospital; 5) prolongs stay in a health care facility; 6) necessitates supportive treatment; 7) significantly complicates diagnosis; 8) negatively affects prognosis; 9) results in temporary or permanent harm, disability, or death."

FDA definition of a serious adverse event (related to drugs or devices)

- Events in which "the patient outcome is death, life-threatening (real risk of dying) condition, hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage."

World Health Organization (WHO) definition of an adverse drug reaction:

- "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

REASONS TO OPTIMIZE ANTIBIOTIC USE:

5. THE GOVERNMENT AND INSURERS DO NOT WANT TO PAY FOR THE CONSEQUENCES OF ANTIBIOTIC OVERUSE

CMS Proposes to Penalize Hospitals with Higher-Than-Expected Rates of Hospital-Acquired Conditions (HACs)

Starting October 2015, the HAC Reduction Program penalizes hospitals in the worst quartile (i.e., more HACs than 75% of other hospitals)

1% payment reduction based on a HAC measure set, which increases over time

For FY 2017 payment determination, these measures have been proposed

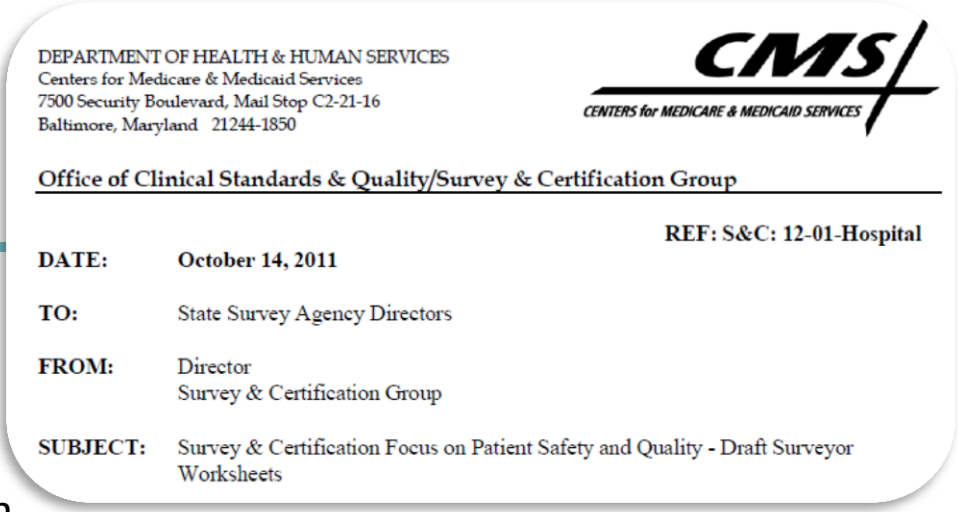
AHRQ Patient Safety Indicators*	CDC Hospital-Acquired Infection (HAI) Measures
• Pressure ulcer rate • Foreign object left in body • Iatrogenic pneumothorax rate • Postoperative physiologic and metabolic derangement rate • Postoperative PE/DVT rate • Accidental puncture & laceration rate	• Central line-associated blood stream infection (CLABSI) • Catheter-associated urinary tract infection (CAUTI) • Surgical site infection (SSI) – SSI following colon surgery – SSI following abdominal hysterectomy • MRSA bacteremia • *Clostridium difficile* infection

While CMS has not yet announced the FY 2017 reporting periods for this program, a hospital's performance <u>in 2014</u> could impact payment in the future†

* CMS is also considering an alternative AHRQ composite measure. † Estimated based on proposed FY 2015 reporting periods, which are calendar years 2012-2013 for CDC HAI measures. CMS: Centers for Medicare and Medicaid Services. HAC: hospital-acquired condition. FY: fiscal year. AHRQ: Agency for Healthcare Quality and Research. CDC: Centers for Disease Control and Prevention. HAI: healthcare-associated infection.

1. 78 Fed. Reg. 91 (May 10, 2013) 27486-27823.

CMS Surveyor Worksheet: Preparation for Metrics



DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

Office of Clinical Standards & Quality/Survey & Certification Group

REF: S&C: 12-01-Hospital

DATE: October 14, 2011

TO: State Survey Agency Directors

FROM: Director
Survey & Certification Group

SUBJECT: Survey & Certification Focus on Patient Safety and Quality - Draft Surveyor Worksheets

- 3 new CMS Surveyor worksheets
- Adopted Oct 2011
- No penalties assessed
- Section 1.C. Systems to prevent transmission of MDROs and promote antibiotic stewardship, Surveillance
- Subsection1.C.2. Can the primary interview participants provide evidence that the hospital has developed and implemented policies and procedures aimed at preventing the development of, and preventing transmission of, MDROs?
  - 1. C.2.a Facility has a multidisciplinary process in place to review antimicrobial utilization, local susceptibility patterns, and antimicrobial agents in the formulary and there is evidence that the process is followed.
  - 1. C.2.b Systems are in place to prompt clinicians to use appropriate antimicrobial agents (e.g., computerized physician order entry, comments in microbiology susceptibility reports, notifications from clinical pharmacist, formulary restrictions, evidenced based guidelines and recommendations).
  - 1. C.2.c Antibiotic orders include an indication for use.
  - 1. C.2.d There is a mechanism in place to prompt clinicians to review antibiotic courses of therapy after 72 hours of treatment.
  - 1. C.2.e The facility has a system in place to identify patients currently receiving intravenous antibiotics who might be eligible to receive oral antibiotic treatment.

National Patient Safety Goals: Reducing Hospital-Acquired Infections

- Focuses primarily on MRSA, VRE, CDI, MDR-GNB, but not inclusive
- National Patient Safety Goals – 3 new requirements
  - NPSG 07.03.01 addresses prevention of HAIs caused by multidrug-resistant organisms (MDROs)
  - NPSG 07.04.01 focuses on preventing catheter-related bloodstream infections
  - NPSG 07.05.01 addresses the prevention of surgical-site infections
- The new requirements focus on the development and implementation of evidence-based best practices, periodic risk assessment, measurement and monitoring of rates of infection, and the education of staff and patients.
- In addition, it is required that hospitals provide goal-related data to hospital leaders, governing bodies, physicians, medical staff, pharmacists, nursing staff, and other clinicians for appropriate action
- In 2009 hospitals will be scored on having met implementation requirements
- Starting January 1, 2010, health systems will be scored on all elements of the goals

Accessible at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/09_hap_npsgs.htm

Health and Human Services Developed Reduction Goals For Select Hospital Associated Infections (HAIs)

The following HAIs, data sources and five year reduction goals were identified[1]

Metric	Source	National 5-year prevention target
Bloodstream infections	NHSN	50% reduction
Adherence to central-line insertion practices	NHSN	100% adherence
***Clostridium difficile* (hospitalizations)**	**HCUP**	**30% reduction**
***Clostridium difficile* infections**	**NHSN**	**30% reduction**
Urinary tract infections	NHSN	25% reduction
MRSA invasive infections (population)	EIP	50% reduction
MRSA bacteremia (hospital)	NHSN	25% reduction
Surgical site infections	NHSN	25% reduction
Surgical Care improvement project measures	SCIP	95% adherence

Steering committee[2]

- Office of Healthcare Quality
- Agency for Healthcare Research and Quality
- Centers for Disease Control and Prevention
- Centers for Medicare and Medicaid Services
- National Institutes of Health
- Indian Health Service
- Health Resources and Services Administration
- Food and Drug Administration
- Office of the Assistant Secretary for Planning and Evaluation
- Office of the Assistant Secretary for Public Affairs
- Office of the National Coordinator for Health Information Technology
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

[1] Department of Health and Human Services website. Available at: http://www.hhs.gov/ash/initiatives/hai/nationaltargets/index.html. Accessed May 30, 2011.

[2] Department of Health and Human Services website. Available at: http://www.hhs.gov/ash/initiatives/hai/actionplan/index.html#state_hai_plans. Accessed May 25, 2011.

REASONS TO OPTIMIZE ANTIBIOTIC USE:

6. PROFESSIONAL SOCIETIES ENDORSE ANTIMICROBIAL STEWARDSHIP

Professional Societies, Government, and Health Organizations Call for "More Action"

AJIC major articles

National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007

Am J Infect Control 2007;35:290-301.

ASHP Statement on the Pharmacist's Role in Antimicrobial Stewardship and Infection Prevention and Control

DEVELOPED THROUGH THE ASHP COUNCIL ON PHARMACY PRACTICE AND APPROVED BY THE ASHP BOARD OF DIRECTORS ON APRIL 17, 2009, AND BY THE ASHP HOUSE OF DELEGATES ON JUNE 16, 2009

Am J Health-Syst Pharm. 2010; 67:575-7

The Joint Commission

2011 Hospital National Patient Safety Goals

IHI.org | A resource from the Institute for Healthcare Improvement

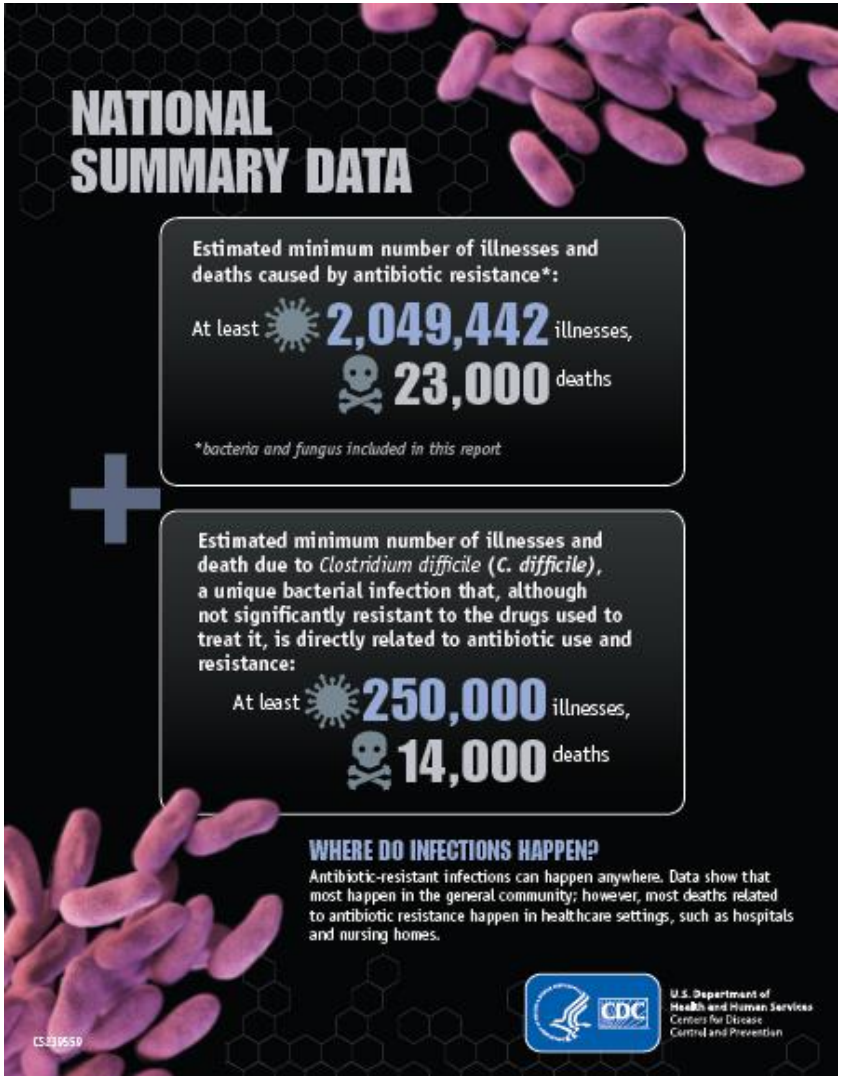
Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

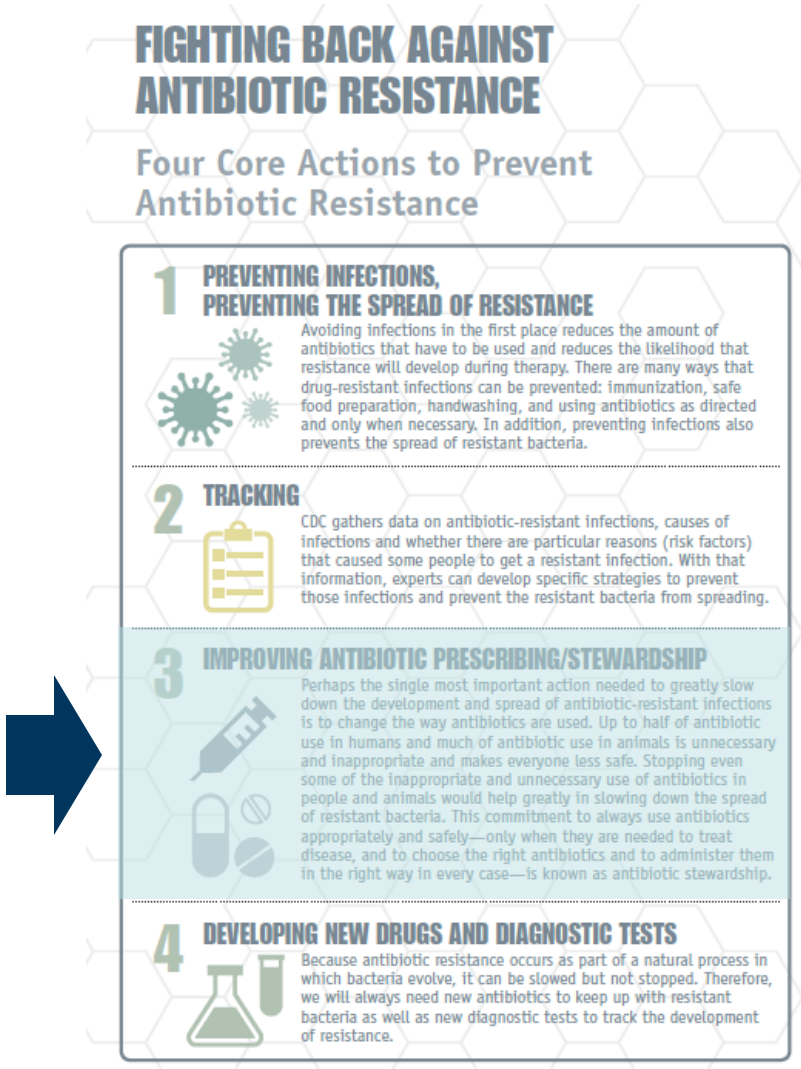
Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Clinical Infectious Diseases 2007; 44:159–77

1058-4838/2007/4402-0001$15.00

Reasons to Optimize Antibiotic Use: The Role of Antimicrobial Stewardship



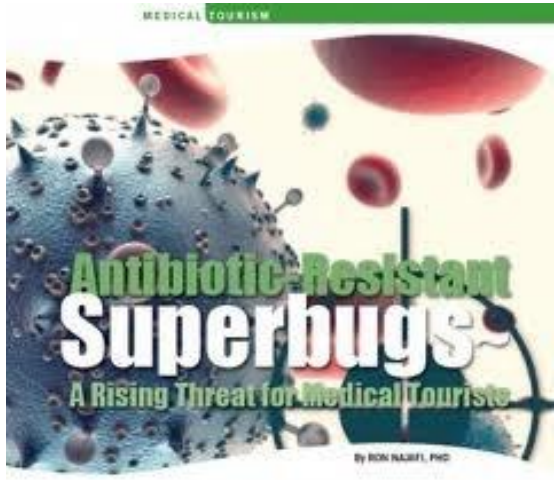


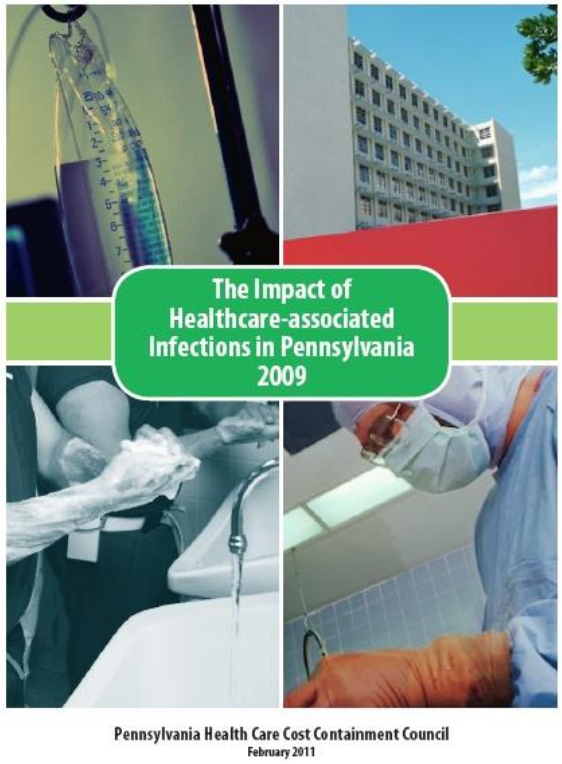
http://www.cdc.gov/drugresistance/threat-report-2013/

REASONS TO OPTIMIZE ANTIBIOTIC USE:

7. PUBLIC MEDIA HAVE MADE CONSUMERS INTO SMART SHOPPERS WHO SEEK SAFE HEALTHCARE DELIVERY

Publically Available Information on Antibiotic Resistance: "A National Call to Action"





REASONS TO OPTIMIZE ANTIBIOTIC USE:

SUMMARY

Benefits of an Antimicrobial Stewardship Program: Beyond Pharmacy Costs (Univ Pennsylvania)

- Main target of program is to improve patient safety through active interventions and healthcare provider education

Outcome	HUP Program (n=96)	Usual Practice (n=95)	Relative Risk (95% CI)
Antimicrobial appropriate	**86 (90%)**	**30 (32%)**	**2.8 (2.1 – 3.8)**
Cure	**52/57 (91%)**	**34/62 (55%)**	**1.7 (1.3 – 2.1)**
Failure	**5 (5%)**	**29 (31%)**	**0.2 (0.1 – 0.4)**
Clinical	0	10 (11%)	--
Microbiologic	0	8 (8%)	--
Superinfection	0	8 (8%)	--
Adverse drug effect	0	2 (2%)	--
Recurrent infection	1 (1%)	1 (1%)	--
Resistance	**1 (1%)**	**9 (9%)**	**0.13 (0.02 – 1.0)**

- Annual savings (600 interventions/month) amounted to $302,400 for antibiotic costs, $533,000 for infection-related costs, and $4.25 million in total hospital costs
- The majority of the cost savings were attributable to a decreased length of stay in the intensive care unit (ICU), although the total hospital length of stay in the study was unchanged

Adapted from: Fishman N. Am J Infect Control. 2006;34:S55-63.

The Need for Antibiotic Stewardship is Now

- Many reasons to control antibiotic use in the hospital setting include:
  - Antibiotic overuse accelerates bacterial resistance (“collateral damage”)
  - Effects of bacterial resistance on medical resources is high
  - Antibiotic resistance is a patient safety issue and is an adverse drug event
  - The “new reality” of hospital-acquired resistant bacterial infections includes penalties from Centers for Medicare and Medicaid (CMS) impacting reimbursement and state reporting mandates
  - Private insurers will follow suit; “value-based purchasing”
- The reality for the future includes:
  - More institutional outbreaks of multidrug-resistant organisms (MDROs), including *Clostridium difficile* infection
  - Few novel antimicrobial strategies to fight MDROs
  - Additional performance measures impacting ability to compete in the hospital marketplace – JCAHO, CMS, IHI, NCQA, CDC, HospitalCompare, NHSN
- Published guidelines and “success stories” employing stewardship strategies exist in great numbers which provide valuable templates

ADDITIONAL PRESENTATION SLIDES

Words to Heed From Decades Past

"…the triumphs of the 'wonder drugs' have been adequately and repeatedly extolled in thousands of medical and lay publications, but the dangers and the harmful sequelae of their uses, and particularly their abuses, have not yet been given sufficient prominence."

"The potentialities for the emergence of races of pathogenic bacteria that are resistant to the available antimicrobial agents by the continuous and widespread use of such agents has already been adequately demonstrated…."

Maxwell Finland and Louis Weinstein. Complications induced by antimicrobial agents. New Engl J Med. 1953;248(6):220-6.

“Despite over 70 years of clinical antibiotic use, bacteria continue to out-perform clinicians by developing increasing levels of resistance to both old and new antibiotics. Just as bacteria continue to adapt, clinicians must continue to adapt their practice”

Roberts J. Crit Care Med 2008;36(8):2433-40.

Accompanying Editorial to Roberts et al [1]

"Given both the frequency of inappropriate antimicrobial use and the association between antimicrobial use and the emergence of resistance, ASPs may help reduce the selective pressure responsible for the emergence and propagation of antimicrobial-resistant pathogens. However, implementation of antimicrobial stewardship programs requires support from hospital leadership, including significant initial financial investments. Studies support the safety, effectiveness, and financial benefits of such programs…." [2]

1 Roberts R, et al. Clin Infect Dis. 2009;49:1175-84
2 Zaoutis T. Clin Infect Dis. 2009;49:1185-6

The Antibiotic Pipeline is Dry

- In the IDSA policy report (July 2004) entitled “Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews,” multiple legislative, regulatory, and funding solutions were suggested

- To address the problem of the dwindling antibiotic pipeline, IDSA launched the “10 × ’20 Initiative” in 2010 calling for development and regulatory approval of 10 novel, efficacious, and safe systemically administered antibiotics by 2020

Bad Bugs Need Drugs

10 × ’20

Ten new ANTIBIOTICS by 2020

Talbot G et al. Clin Infect Dis. 2006;42:657-68; Boucher H et al. Clin Infect Dis. 2009;48:1-12; Infectious Diseases Society of America (IDSA); Spellberg B, Blaser M, et al. Clin Infect Dis 2011; 52(suppl 5):S397–428; Boucher H et al. Clin Infect Dis. 2013;56(12):1685-94

Many Scientific Policy Groups Have Expressed Concern for Increasing Antibiotic Resistance

- Infectious Diseases Society of America (IDSA) and "Bad Bugs, No Drugs" policy report (July, 2004)
  - Expressed concern for the decreasing activity in new antibiotic development [1]
  - Identified several problematic bacterial pathogens , including *Acinetobacter baumannii*, ESBL-producing *Enterobacteriaceae*, MRSA, *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus faecium* [2]
  - Antimicrobial Availability Task Force (AATF) pursues solutions to the lack of drug research and development as a political action committee for IDSA
- Society for Healthcare Epidemiology of America (SHEA) launches Antimicrobial Stewardship initiative [3]
- Centers for Disease Control and Prevention (CDC) launches "Get Smart for Healthcare" campaign
  - Includes state Antimicrobial Stewardship Programs (ASPs), training and educational materials, slide sets, HAI prevention tools, gap analyses, champion statements, business plans, certification program links (Society of Infectious Diseases Pharmacists, SIDP; Making a Difference in Infectious Diseases, MAD-ID), drug utilization study forms, antibiotic order sheets, best practice websites [4]
  - CDC launches National Antimicrobial Use Benchmarking program via NHSN Antibiotic Use and Resistance module (2011) [5]

SHEA
The Society for Healthcare Epidemiology of America

CDC

1 Infectious Diseases Society of America. *Bad Bugs, No Drugs*. July 2004. Available at: www.idsociety.org
2 Talbot GH et al. *Clin Infect Dis* 2006;42:657-68 3 http://www.shea-online.org/news/stewardship.cfm
4 http://www.cdc.gov/getsmart/healthcare/improve-efforts/resources/index.html#ASTrO
5 http://www.cdc.gov/nhsn/psc_ma.html

The Burden of Antimicrobial Resistance

- Bacterial resistance limits the choice of antibiotics which might be effective, often relying on newer and more expensive antibiotics to treat infections
- Infections due to antibiotic-resistant pathogens have negative clinical and economic consequences compared to infections due to antibiotic-susceptible pathogens [1,2]

Outcomes	Methicillin-susceptible *S aureus*[1*] (n = 165)	Methicillin-resistant *S aureus*[1*] (n = 121)	Imipenem-susceptible *P aeruginosa*[2] (n = 719)	Imipenem-resistant *P aeruginosa*[2] (n = 135)
Mortality	6.7%	20.7%[a]	16.7%	31.1%[b]
Median Hospital Charges	$52,791	$92,363[a]	$48,381	$81,330[c]
	[a] p < 0.001		[b] Relative risk, 1.86; 95% CI, 1.38-2.51; [c] p < 0.001	

- As bacterial resistance increases, the accurate selection of appropriate empiric therapy decreases
- Studies have demonstrated that inappropriate initial therapy is an important independent determinant of mortality [3-6]

1 Engemann JJ, et al. Clin Infect Dis 2003;36:592-598. 2 Lautenbach E, et al. Infect Control Hosp Epidemiol 2006;27:893-900. 3 Ibrahim EH, et al. Chest. 2000;118:146-155. 4 Valles J, et al. Chest. 2003;123:1615-1624. 5 Khatib R, et al. Eur J Clin Microbiol Infect Dis 2006;25:181-185. 6 Teixeira PJZ, et al. J Hosp Infect 2007;65:361-367.

The Impact of Healthcare-Associated Infections (HAIs) in the USA

- The Centers for Disease Control and Prevention (CDC) estimates that 1.7 million patients contract healthcare-associated infections every year and nearly 99,000 of them die [1,3,4]
  - HAIs are estimated to be one of the top 10 causes of death in the US
- The annual direct medical costs of HAIs to hospitals range from $28.4 to $33.8 billion [2,3,4]
  - A study of 1.7 million hospitalized patients discharged from 77 hospitals found that the additional cost of treating a HAI averaged $8,832
- In Pennsylvania, 23,287 (1.2%) hospital-admitted patients contracted at least one HAI during their stay[5]
  - Mortality: 9.4% (HAI) vs 1.8% (no HAI)
  - Avg LOS: 21.6 days (HAI) vs 4.9 days (no HAI)
  - Estimated Medicare payments: $20,471 (HAI) vs $6,615 (no HAI)
  - Readmission within 30 days (infection/complication): 29.8% (HAI) vs 6.2% (no HAI)

1 Klevens R, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Reports. 2007;122:160-166
2 Scott, RD. The direct medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention, 2009. Division of Healthcare Quality Promotion, National Center for Preparedness, Detection, and Control of Infectious Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, 2009.
3 GAO Report; April 16, 2008; GAO-08-283; HHS Action Plan to Prevent HAIs; released Jan 6, 2009
4 http://www.ihi.org/IHI/Programs/Campaign/Campaign.htm?TabId=2#InterventionMaterials
5 The Pennsylvania Department of Health. (2010). Healthcare-associated infections (HAI) in Pennsylvania hospitals – 2009 (technical report).

Payment Policies for Nosocomial Infections

Nosocomial infections for which payers will no longer provide extra reimbursement				
Payer	**Catheter-associated urinary tract infections**	**Vascular catheter-associated infections**	**Surgical Site Infections**	
			Medistinitis after CABG surgery	**After elective orthopedic procedures and bariatric surgery for obesity**
Medicare	No additional payment (Oct 2008)	No additional payment (Oct 2008)	No additional payment (Oct 2008)	No additional payment (Oct 2008)
CIGNA	No payment	No payment	No payment	Payment
Wellpoint	No payment	No payment	No payment	Payment

Other payers are beginning to take steps that would eliminate hospital payments for 28 “never events” endorsed by the National Quality Forum (NQF). Although nosocomial infections are not included in the initial NQF list of these “never events” they may be added in the future.

McQuillin D, et al. Clin Infect Dis. 2008;47:1051-63